REMARKS

This responds to the Office Action mailed on February 2, 2009.

Claims 1, 4-5, 7 and 9-13 are amended and claim 6 is canceled. Claims 1-5 and 7-14 are pending in this application.

The Examiner objected to claims 1-7 and 9-10 stating that the claims contain the acronym "iscom" and requesting the acronym be capitalized in the first recitation and include the full recitation followed by the acronym in parenthesis. Applicant has the amended the claims as required by the Examiner. Applicant respectfully submits that the amendment renders the objection moot and respectfully requests withdrawal of the objection of claims 1-7 and 9-10.

The 35 U.S.C. § 112, First Paragraph, Rejection

Claims 11-13 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Applicant respectfully submits that the amendment to claims 11-13 renders the rejection moot. Thus, Applicant respectfully requests withdrawal of the rejection of claims 11-13 under § 112(1).

The 35 U.S.C. § 112, Second Paragraph, Rejections

Claims 1, 4-7 and 11-13 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant respectfully traverses this rejection.

With regards to claims 1 and 4-6, Applicant respectfully submits that the amendments to claims 1 and 4-6 renders the rejection moot. Therefore, Applicant respectfully requests withdrawal of the rejection of claims 1 and 4-6.

With regards to claims 1, 5, 7 and 11-13, the Examiner alleges that the skilled artisan would not be readily apprised of the metes and bounds of the phrase "fragment A of Quil A" as this term is not a recognized term nor defined in the specification. Applicant respectfully submits that the claims recite "fraction A of Quil A" and not "fragment." Additionally,

Applicant respectfully submits that the phrase "fraction A of Quil A" is an art recognized term and is defined in the specification. For example, in lines 1-5 of WO 2005/002620 (corresponding to the instant application) it is mentioned that fraction A is described in WO 96/111711, which is the cited Cox patent application, and in EP 0 436 620. Additionally, at page 8, lines 12-22, of the instant application as originally filed it is disclosed that fraction A is prepared from the lipophilic fraction obtained on chromatographic separation of crude aqueous extract and elution with 70% acetonitrile in water to recover the lipophilic fraction. The lipophilic fraction is then separated by semipreparative HPLC with elution using a gradient of from 25% to 60% acetonitrile in acidic water. The fraction referred to herein as "Fraction A" or "QH-A" is the fraction which is eluted at approximately 39% acetonitrile. Thus, Applicant respectfully submits that the metes and bounds of the phrase "fragment A of Quil A" is definite. Therefore, Applicant respectfully requests withdrawal of the rejection of claims 1, 5, 7 and 11-13.

Regarding claims 11-13, the Examiner stated that there was insufficient antecedent basis for the phrase "fragment A of Quil A" in the claim. Applicant respectfully submits that the amendments to 11-13 renders this rejection moot. Applicant respectfully requests withdrawal of the rejection of claims 11-13.

Applicant respectfully submits that the claims comply with 35 U.S.C. § 112, first and second paragraph. Thus, Applicant respectfully requests withdrawal of these rejections.

The 35 U.S.C. § 102(b) Rejection

Claims 1-2, 4-9 and 14 were rejected under 35 U.S.C. § 102(b) as being anticipated by Friede et al. (U.S. Patent No. 6,558,670 Publication Date May 6, 2003). Applicant respectfully traverses this rejection.

1) Saponin fraction A of Quil A, which must be present in Applicant's invention, differs from the closest fraction (QS 7) mentioned, but not tested or preferred, in Freide et al.

Page 4 of the instant Office states that "Friede et al does not differ in any way." Applicant respectfully submits that this statement is incorrect. Applicant respectfully submits that there is a difference in the saponin fraction A of Quil A, which must be present in Applicant's invention, and the closest fraction QS 7 mentioned, but not tested or preferred, in Freide et al.

The present invention relates to the use of fraction A of Quil A. In the event that the present invention is used together with the oligonucleotide CpG as the at least one other adjuvant, it may be looked upon as a selection invention of Friede et al., i.e. a selection from saponins generally mentioned in Friede et al. However, in the Friede et al. patent, haemolytic saponins are preferred (see below) and the essential saponin of the present invention, fraction A of Quil A, is not haemolytic, *nor mentioned* in Friede et al. One saponin mentioned in Friede et al. is fraction QS 7 of Quil A. Fraction QS 7 is enclosed in fraction A of Quil A. However, fraction A also contains saponins other than QS 7.

Fraction A is composed of several Quil A saponins among them QS 4, 5, 6 and 7, see US Pat No. 5,057,540 (Kensil et al.; enclosed herewith for the Examiner's convenience). Fraction A is shown in Enclosure 1 (enclosed herewith), which is a HPLC diagram of fraction A and C prepared by the Applicants. Fraction A, is prepared from the lipophilic fraction obtained on chromatographic separation of the crude aqueous Quil A extract and elution with 70% acetonitrile in water to recover the lipophilic fraction. The lipophilic fraction is then separated by semipreparative HPLC with elution using a gradient of from 25% to 60% acetonitrile in acidic water. The fraction referred to herein as "Fraction A" or "QH-A" is the fraction which is eluted at approximately 39% acetonitrile (please see the cited Cox application WO 96/111711, page 7 lines 21-30).

The QS 7 fraction was prepared from aqueous extracts of the Quillaja saponaria Molina bark which were dialyzed against water. The dialyzed extract was lyophilized to dryness, extracted with methanol and the methanol-soluble extract was further fractionated on silica gel chromatography and by reverse phase high pressure liquid chromatography (RP-HPLC) USP 5, 0570, 540 column 4 lines 55-63. FIG. 3 shows the comparison of Superfos "Quil-A" and dialyzed methanol soluble bark extract by HPLC.

FIG. 5B demonstrates the purity of QA-7, QA-17, QA-18, and QA-21 by normal phase (5B) thin layer chromatography.

Fraction A of Quil A is obtained by a different method than the fraction QS7 and is more crude in that it among other fractions also comprises fraction QS 7.

2) Saponin fraction A of Quil A of the present invention has a different effect than fraction QS 7 mentioned, but not tested or preferred, in Friede et al.

As mentioned, Friede et al. specifically state that heamolytic saponins are preferred. This is disclosed in column 2, lines 61-63, "particularly wherein said saponins have heamolytic activity. Preferred saponins include Quil A, QS 1, QS 21, QS 7...." Further, it is stated in column 4, line 66 to column 5, line 4, "[f]or the purposes of this invention the saponin adjuvant preparation is haemolytic if it lyses the erythrocytes at a concentration of less than 0.1%. As means of reference, substantially pure samples of Quil A, QS21, QS7, Digitonin, and β-escin are all haemolytic saponins as defined in this assay." In column 5, lines 13-15, it is once again stated that "[t]he final formulations in the form as they are administered to the mucosal surface of the vaccine are preferably haemolytic in nature." Finally, at the end of the example in column 12, lines 10-12, "taken together, these results show clearly the potential of intranasal formulations combining a lytic saponin and an immunostimulant."

Thus, it is submitted that as Friede et al. prefer haemolytic formulations, ISCOMs are not at all suitable. A present inventor, Morein, and other experts have described in numerous articles that the haemolytic activity of the saponins is abolished by the incorporation into ISCOM structures. This is evident from Drane et al., *Expert Rev Vaccines* 6(5), 772, 2007 (page 762 left column lines 22-25; a copy of which is enclosed herewith for the Examiner's convenience).

Furthermore, fraction A of Quil A used according to the present invention is not haemolytic. This is evident from the cited Cox document (WO 96/11711). Table 1 on page 8 of WO 96/11711 shows that fraction A has very low haemolytic activity. Additionally, fraction A of Quil A is integrated into an ISCOM according to the present invention, which makes even haemolytic saponins non-haemolytic.

3) Saponin fraction A of Quil A that must be present in Applicant's invention differs from the saponin QS 21 disclosed, preferred and tested by Friede et al.

Applicant respectfully submits that there is a difference in the saponin fraction A of Quil A that must be present in Applicant's invention and the saponin QS 21 disclosed, preferred and tested by Friede et al.

Fraction C of Quil A comprises fraction QS 21 tested in the example of the Friede et al. patent. However, fraction C also contains saponins other than QS 21. Fraction A, which must be comprised in the composition according to the present invention, is quite another fraction of Quil A than fraction C or QS 21.

It has been presented above how fraction A is produced according to the instant disclosure and the cited Cox document (WO 96/11711). Enclosure 1 shows that fraction C comprises fraction QS 21 and also other fractions of Quil A. In the cited Cox document (WO 96/11711) at page 7, line 21 to page 8, line 2, it is described that fraction C is produced like fraction A, but is eluted at approximately 49% acetonitrile. Therefore, it is evident that fraction C is different from fraction A.

Further, US Pat. No.5,057,540 describes at column 4 and 5 and in Example 1 that fraction QS 21 is prepared as fraction QS 7 but is obtained as a later fraction with higher retention time. It is evident that fraction QS 21 which is a saponin fraction comprised in fraction C is different from fraction A.

4) Saponin fraction A of Quil A, which must be present in Applicant's invention, has another effect than saponin QS 21 disclosed, preferred and tested by Friede et al.

Fraction A of Quil A used according to the present invention is not haemolytic. This is evident from the cited Cox document (WO 96/11711). Table 1 on page 8 of WO 96/11711 shows that fraction C, which is close to QS 21, has high haemolytic activity. This is also the saponin that Friede et al. prefer and use.

In column 2, lines 19-22, Friede et al. refer to the haemolytic saponins QS21 and QS17 of US Pat. No. 5,057,540. Figure 10 of US Pat. No. 5,057,540 shows that QS21 and 17 are indeed haemolytic at around 10 μg/ml.

Another difference between fraction A of Quil A and fraction QS 21 preferred and tested in Friede et al. is the type of immunological reaction induced. In the response dated October 27, 2008, Applicant provided an attachment titled "Intranasal administration of PR8 micelles," which provided results from an assay in which the Applicant tested fraction A and C from Quil A in an intranasal administration of fraction A and C of Quil A in free form. It is evident from the results that Fraction A of Quil A does not improve the IgA titre (columns 2, 3 and 4 of the figure) after intranasal administration. This example confirms the intranasal adjuvant effect of Fraction-C, which comprises fraction QS 21 and other saponins. However, no such effect is shown with Fraction-A. Applicant has provided herewith a declaration executed by Karin Lovgren, one of the inventors, so as to have the Examiner fully consider this evidence.

Therefore, Applicant respectfully submits that claims are novel in view of Friede et al. Thus, Applicant respectfully requests withdrawal of the rejection under § 102(b).

The 35 U.S.C. § 103(a) Rejection

Claims 1-14 were rejected under 35 U.S.C. § 103(a) as being obvious over Friede et al. (U.S. Patent No. 6,558,670) in view of Cox et al. (WO 96/11711). Applicant respectfully traverses this rejection.

Friede et al. disclose that that immune-stimulatory oligonucleotides (CpG) and saponin combinations are potent adjuvants (col. 3 l. 25-27). Friede et al. specifically state that heamolytic saponins are preferred (see, for example, column 2, lines 61-63, column 4, lines 66 to column 5, line 4, and column 5, lines 13-15). Fraction A of Quil A is not mentioned at all in Friede et al.

Fraction A of Quil A is not haemolytic. This is evident from the cited Cox patent application WO 96/11711. Table 1 on page 8 of WO 96/11711 shows that fraction A has very low haemolytic activity. Consequently Friede et al. teaches away from using fraction A of Quil A, as fraction A is not heamolytic.

Applicant respectfully submits that a skilled person reading Friede et al. which discloses that haemolytic saponins are preferred would not consider using fraction A upon reading Cox. Therefore, the skilled person would not combine Friede et al. with Cox.

Even if, for the sake of argument, the skilled person would revert to Cox if considering using fraction A of Quil A as an adjuvant together with another adjuvant, the skilled person would *not* consider using fraction A and fraction C in different ISCOM particles or with fraction A integrated into an ISCOM particle and fraction C in free form. The Cox patent only relates to the integration of fractions in the same ISCOM complex.

Friede mentions that the saponin may be in the form of ISCOM col. 5 lines 8-10. However, experts have described in numerous articles that the haemolytic activity of the saponins is abolished by the incorporation into ISCOM structures. Thus, even in mentioning ISCOM, Friede et al. teach away from using ISCOMs, as Friede et al. clearly state that haemolytic saponins are preferred.

Thus, the claims are not obvious over Friede et al. (U.S. Patent No. 6,558,670) in view of Cox et al. (WO 96/11711). Therefore, Applicant respectfully requests the withdrawal of the rejection under 103(a).

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's representative at (612) 373-6905 to facilitate prosecution of this application.

If necessary, please charge any additional fees or deficiencies, or credit any overpayments to Deposit Account No. 19-0743.

Respectfully submitted,

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being filed using the USPTO's electronic filing system EFS-Web, and is addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 11TH day of August, 2009.

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